Remarks

Applicants thank the Examiner and her Supervisor for the interview on April 24, 2008. A summary of the interview is provided below. Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are pending in the present application. Claims 1 and 26 have been amended. The following objections and rejections are at issue and are set forth by number in the order in which they are addressed:

1. The claims are rejected for double patenting;
2. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al.;
3. Claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-34 and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Burns et al.;
6. Claims 1-10, 12, 14, 18, 20, 21, 26, 28, 30-38 and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Schroder et al.;
7. Claims 1-10, 12, 14, 18, 20-24, 26, 28, 30-34, and 39-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.;
8. Claims 1-10, 12, 14, 18, 20, 21, 25, 28 and 30-34 and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Naldini et al.

Claims 1 and 26 have been amended in order to further Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. None of the claim amendments made herein are intended to narrow the scope of any of the amended claims within the meaning of *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*,

234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

1. Summary of Interview

Applicants thank Examiner Popa and her SPE, Examiner Woitach, for the interview on April 24, 2008. For the Applicants, Mitchell Jones and Dr. Gregory Bleck attended. The following topics were discussed:

- The Examiners and Applicants engaged in a discussion centered on a draft of the Declaration of Dr. Bleck and the references addressed in that Declaration, which are attached to the Bleck Declaration being submitted herewith. For the reasons stated in the Declaration, Dr. Bleck established that the state of the art prior to the filing date of the present application discouraged a person of skill in the art from attempting the claimed methods. In particular, Dr. Bleck established that those of skill in the art would not attempt to use the claimed invention because the state of the art was that multiple inserts of a retroviral vector would be down-regulated due to viral interference, gene silencing and methylation. Thus, the state of the art was that introducing multiple retroviral vectors into a cell line would have the effect of decreasing expression of a desired gene, not increasing expression as documented in the specification. As a result, persons of skill in the art would be discouraged from introducing the claimed number of retroviral vectors into a cell as claimed.
- The parties also discussed the Examiner's use of Kustikova and Zielske in the rejection. Applicant's noted that Kustikova and Zielske were published after the Applicant's priority dates, and thus could not be properly used to rebut the Applicants arguments with respect to the state of the art prior to Applicant's filing date. The Examiner did not dispute that Kustikova and Zielske were published after Applicant's priority date.
- Examiner's Popa and Woitach argued that the references relied on by the Applicants to establish the state of the art were gene therapy references and did not apply broadly to the use immortalized tissue culture cells. The Examiner's indicated that limiting the claims to the use of immortalized cell lines would

entitle the Applicants arguments as presented in the Bleck Declaration to more weight.

- Examiner Woitach indicated that because of informal discussions with other Examiners, he had come to the conclusions that the invention as claimed was not patentable. Applicants note that these discussions have not been made of record.

2. Double patenting.

Applicants have filed a terminal disclaimer over the cited patents.

3. The claims are not obvious over Mathor, Felts and Inaba.

Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al. Applicants respectfully traverse.

Applicants have amended the claims consistent with the Examiner's recommendation to be directed to the use of immortalized cell lines. Applicants note that Mathor, Felts and Inaba are directed to gene therapy uses and infection of primary cell cultures. The references do not teach or suggest the use of immortalized cells as presently claimed.

Applicants next respectfully submit that in the April 24 interview, the Examiners argued that Applicants were relying on gene therapy references to establish the state of the art, and that those references did not apply to the of immortalized cell lines for the production of recombinant proteins. Applicants disagree for the reasons outlined below. Nevertheless, Applicants respectfully note that if the gene therapy references cited by Applicants are not applicable to the use of immortalized cell lines for recombinant protein production, then gene therapy references are not applicable to the current claims which are limited to the of immortalized cell lines, i.e., those references are non-analogous art.

For the reasons cited in the Bleck Declaration, Applicants respectfully submit that a person of skill in the art would not have thought to introduce greater than 20 retroviral vectors into an immortalized cell line to produce recombinant protein because they would have thought that protein production would be decreased due to viral interference, gene silencing or methylation. Thus, Applicants proceeded contrary to the established state of the art in seeking to

make cell lines in which the cells contain more than 20 integrated retroviral vectors. See MPEP 2145(X)(D)(3).

In Dr. Bleck's previous Declaration, he stated that references such as Arai et al., Virology 260:109-115 (1999) and Coffin et al., Development and Applications of Retroviral Vectors, Chapter 9 in Retroviruses, 1997, p. 437-473, specifically teach away from the current claims and that one of skill in the art would be "discouraged" from using a the claimed multiplicity of infection and copy insert number to obtain cells for the production of a secreted protein.

As a preliminary matter, the Examiner has attempted to rebut the evidence in the Bleck Declaration primarily by relying on the Kustikova and Zielske references in pages 15 and 16 of the Office Action. At page 22 of the Office Action, the Examiner indicates that Kustikova and Zielske are "prior art made of record." Applicants vigorously contest the characterization of these references as prior art. In the interview, the Examiner's acknowledged that the references were not prior art. This issue is addressed in Paragraph 6 of the Bleck Declaration. In fact, both references were published well after either the filing date of the parent application (filed June 29, 2001), which contains support the serial transduction limitations and integration ranges claimed in this application, or the instant application, filed January 16, 2004. As stated by Dr. Bleck, Kustikova and Zielske were published well after the disclosure in my original patent application. Contrary to the Examiner's assertions, these references confirm to a person of skill the art the uncertainty that was associated with introducing multiple copies of a retroviral vector into a host cell.

At pages 13-14 of the Office Action, the Examiner addresses the Dr. Bleck's previous Declaration with respect to the teachings of Arai et. al. and Coffin et al. With respect to Arai et al., the Examiner states:

> Arai et al. teach that the number of proviral integrations (and therefore, protein production) can be increased by increasing MOI (p. 112, column 1, Fig. 3) and that 15 integrations can be obtained with an MOI of 30. Although they teach that proviral integration with a very high copy number seems to cause cell death, Arai et al. do teach that not cells [sic] are dying and therefore, one of skill in the art would have known to use routine experimentation to clone the viable cells that contain a very high number of integration events and produce cell lines that synthesize high amounts of recombinant protein. Therefore, the art does not teach away from the claim

> invention. . . . One of skill in the art would use only routine experimentation to optimize the results, and by doing this one of skill in the art would have necessarily obtained integrations within the broad range of 10 to 100."

According to Paragraph 4 of the Bleck Declaration, "the Examiner makes several assumptions here that are either scientifically incorrect or that have a better scientific explanation. First, the examiner assumes that the cells that do not die have a very high copy number of integrated vectors. There is no evidence for this. Arai did not clone or determine the number of integrated vectors in those cells. Second, a person of ordinary skill in the art would expect that the surviving cells did not have high numbers of integrations. Retroviral vectors do not transduce cells that are not dividing. The most reasonable explanation is that the surviving cells were not undergoing cells division during the transduction period and thus did not become transduced or that the cells were at point in the cells cycle so that they were not exposed to vector at the optimum time period for transduction and thus only had low numbers of integrations. A person of skill in the art would believe that this is a valid explanation, especially when Arai teaches that the major factor for apoptosis was probably a high number of integrations and insertional mutagenesis."

> With respect to Coffin et al., the Examiner states:
>
> Regarding the argument that Coffin teaches that insertional mutagenesis by retroviral vectors in the instant case, because the claims encompass a host cell in vitro and the combined teachings of Mathor et al. and Felts et al. are drawn to the in vitro production recombinant proteins. Applicant's argument that the teachings of high numbers of integrations and insertional mutagenesis would apply both in vivo and in vitro is not found persuasive because Coffin et al. refers to gene therapy in humans where malignant transformation can endanger the patient life, which cannot be compared to a cell in culture, wherein malignant transformation does not endanger anybody's life and does not impede the cell from producing the protein of interest (also see below).

Dr. Bleck addresses this issue in Paragraph 5 of his Declaration: "Coffin et al. confirms the teaching of Arai et al. that the incorrect use of retroviral vectors can lead to insertional mutagenesis. Furthermore, the Examiner's assumption that malignant transformation or other mutagenesis would not impede an immortalized mammalian cell from producing a protein of interest has no scientific basis. In fact, if an immortalized mammalian cell is mutagenized or transformed in some way by the vector, it is almost certain that production of the desired protein

would be affected. The recombinant protein production industry relies on the use of standardized immortalized mammalian cells whose growth is predictable. Cells with additional mutations would be highly undesirable."

The Bleck Declaration further presents additional evidence that establishes that the present invention proceeded contrary to the accepted wisdom in the art. First, a person of skill in the art reading Kustikova would be discourages from attempting to use the claimed methods because "Kustikova actually shows is that those of skill in the art would have been discouraged from intentionally making cell lines with high numbers of retroviral integration because of insertional mutagenesis." Bleck Decl., Para. 7. Likewise, Zielske found that transgene expression reach a plateau after four integrations. To a person of skill in the art, "this further teaches away from the claimed methods – if only four integrations are needed for maximum expression, why introduce more? As shown in the next paragraphs, those of skill in the art believed that expression reached a plateau because of viral interference, gene silencing or methylation." Bleck Decl., Para. 8.

The Bleck Declaration also provides two additional references that demonstrate that the inventors proceeded contrary to the accepted wisdom in the art. Walker et al., Human Gene Therapy. Jun 1996, Vol. 7, No. 9: 1131-1138 (Tab 1), teaches that: "Simultaneous retroviral transductions were infrequent events. In addition, transduction of previously infected cells (sequential transductions) occurred at lower than expected frequencies. Our data suggest that there is quantifiable viral interference in sequential retroviral transductions. This interference occurs by a mechanism that appears to be independent of the amphotropic retroviral receptor." Likewise, Bestor, J. Clin. Invest., 105(4):409-411 (2000) teaches retroviruses and repeated genes are often silenced or suppressed by mammalian cells. According to a Dr. Bleck, "because of viral interference and gene silencing or suppression, a person of ordinary skill in the art would be discouraged from using sequential transductions to increase viral inert number and would be discouraged from attempting to create immortalized mammalian cell lines with the claimed number of insertions."

In the Interview on April 24, 2008, the Examiner and the Examiner's supervisor indicated that the teachings Kustikova, Zielske, Walker and Bestor were related to gene therapy and thus not applicable to immortalized mammalian cell cultures. Dr. Bleck disagrees with this

because the prior art concern with viral interference, gene suppression and gene silencing would apply regardless of the situation was gene therapy or making immortalized mammalian cells to produce a protein of interest. As Dr. Bleck notes, "if it is the Examiner's position that those references only apply to gene therapy situations, then gene therapy prior art references such as Mathor et al., which addresses the use of normal human keratinocytes for gene therapy, Felts et al., which addresses "fields for which highly efficient gene delivery is essential" and refers specifically to gene therapy, and Inaba et al., which addresses the use of endothelial cells for gene therapy (as well as Kustikova and Zielske), do not apply to the use of retroviral vectors in immortalized mammalian cells such as those exemplified throughout the patent application."

Applicants further note that the Examiner's assertions with respect to Mathor et al. are misplaced. In particular, in the Interview the Examiners indicated that this Table shows that increasing the number of integrations increases protein production. According to Dr. Bleck, "a person of ordinary skill in the art would not interpret the data in that manner. The data shows that at 8 integrations, 1140 ng/10^6 cells/day of protein is produced, and that when 15 integrations were obtained, the protein production decreased to 1014 ng/10^6 cells/day or protein produced. This indicates that protein production had reached a plateau and that further introduction of retroviral vectors did no good or decreased protein production. Thus, one of skill in the art would conclude from the data additional integration past 8 integrations were not needed or not desirable."

For the foregoing reasons, Applicants respectfully assert that the claims are not obvious over the combination of Mathor, Felts and Inaba and that any *prima facie* case of obviousness established by the Examiner (and Applicants assert that none has been established) is rebutted by the evidence in the Bleck Declaration. This evidence is also directly applicable to the Examiner's assertion that "the art teaches the number of integrations per cell as being a result-effecting variable and therefore, one of skill in the art would be motivated to use a range of integrations (obtained by varying MOIs) to obtain optimum results." The evidence presented above establishes that, contrary to the Examiner's assertions, a person of skill in the art would be discouraged by the state of the art from introducing from 20 to 100 retroviral vectors into an immortalized cell.

Applicants further note that each of the 35 U.S.C. 103 rejections is based on the

combination of Mathor, Felts and Inaba, thus the arguments and evidence presented above reject each of the current 35 U.S.C. 103 rejections because Burns, Schroder, Primus and Kolb and Naldini do not cure the defects noted. In particular, Schroder does not cure the defects with respect to methods of introducing multiple copies of retroviral vectors into immortalized cells such as CHO cells. Moreover, by the Examiner's own reasoning, gene therapy papers such as Mathor, Felts and Inaba are non-analogous art to references or claims which are directed the use of immortalized cells to make recombinant proteins. Thus, Mathor, Felts and Inaba are not properly combinable with Schroder which completely fails to address transduction of any type of cell with a retroviral vector. As a result, Applicants respectfully submit that the claims are allowable over Mathor in views of Felts and Inaba et al., in further view of Schroder et al.; Mathor in views of Felts and Inaba et al., in further view of Burns et al.; Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.; and Mathor in views of Felts and Inaba et al., in further view of Naldini et al. Applicants respectfully request that these grounds of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

CONCLUSION

All grounds of rejection and objection of the Office Action of November 28, 2007 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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